DRAFT

National Institute of Environmental Health Sciences
"New Frontiers in Environmental Sciences and Human Health: The 2006-2011 NIEHS Strategic Plan"

Introduction

The preparation of this Strategic Plan for the National Institute of Environmental Health Sciences (NIEHS) would not have been possible without the concerted efforts of many dedicated individuals within the Institute and in the extended extramural community of investigators, clinicians, and interested public citizens. Their dedication and commitment to the environmental health sciences, and to enhancing our understanding of environmental exposures and their impact on the origins and treatment of human disease drives the work of this institution, and is the foundation of all that we aspire to achieve. Among many, the members of the NIEHS National Advisory Environmental Health Sciences Council deserve particular recognition for their leadership in providing critical and objective guidance to the Institute.

Today, we find ourselves at a critical junction where new tools and opportunities for substantial scientific achievement intersect with our growing understanding of cellular and molecular mechanisms by which environmental exposures exert their effects. The potential for advances in our nation's health and the consequent challenge to environmental health sciences have never been greater.

To take advantage of these opportunities, we at NIEHS are committed to ensuring that our programs are focused, relevant, dynamic, and timely. This is the essence and the theme of this Strategic Plan for NIEHS – to convey our strategy and determination to ensure that the work sponsored and initiated by the Institute, both intramurally and extramurally, concentrates in areas with the greatest potential for value and benefit. Achieving our mission will require persistence, a fundamental commitment to good, sound science, and a broad application of environmental sciences to further our understanding of human biology and human disease. Our success will be measured in the disease and suffering that our scientific advances will be used to prevent. That is our obligation to the nation.

I was personally involved in each step of the strategic planning process, and am fully committed to the goals outlined in this document. With this blueprint as a foundation, there is much we intend to achieve as we venture into new avenues to advance the application of environmental sciences to human health. However, this plan is only the starting point. If we're to succeed, we'll need to remain nimble and responsive to opportunities and challenges that are currently unforeseen. One thing is certain, we will need you to work with us to fully achieve the potential of the NIEHS.

Sincerely,

David Schwartz, MD
Director, NIEHS

The NIEHS Strategic Planning Process: An Overview

The development of the NIEHS Strategic Plan followed a detailed and accelerated timetable beginning in the Spring of 2005, and engaged a broad spectrum of individuals – investigators, clinicians, other scientists, engineers, policy advocates, and interested citizens – in providing their perspectives and opinions to the Institute. The initial step in the process was an invitation to NIEHS stakeholders to help identify promising areas of need and opportunity in the environmental health sciences, as well as to suggest new potential directions for NIEHS and its research programs. Key milestones in the planning sequence included the following major initiatives and events:

- NIEHS staff, headed by Deputy Director Dr. Sam Wilson in collaboration with Dr. Sheila Newton, Director of the Office of Science Policy and Planning, and with additional input from area investigators in the Research Triangle, formed a Strategic Planning Working Group to develop the procedures, format, and timetable for the overall strategic planning process.

- Following an announcement in the Federal Register, a six-question web survey was posted on the NIEHS website between June 22 and August 5, 2005. The questions posed were:
    - What are the disease processes and public health concerns that are relevant to environmental health sciences?
    - How can environmental health sciences be used to understand how biological systems work, why some individuals are more susceptible to disease, or why individuals with the same disease may have very different clinical outcomes?
    - What are the major opportunities and challenges in global environmental health?
    - What are the environmental exposures that need further consideration?
    - What are the critical needs for training the next generation of scientists in environmental health?
    - What technology and infrastructure are needed to fundamentally advance environmental health science?

  Over 400 responses were received from scientists and clinicians in universities, other research institutions, and government, as well as from advocacy groups and individual citizens. NIEHS staff worked at length to document all the input into a single summary document.

- Using the input from the web survey, six broadly-defined discussion topics were identified as being central to strategic decision-making on the future direction, emphasis and priorities of NIEHS programs.

- In September, senior NIEHS made a detailed presentation on the strategic planning process at the scheduled meeting of the NIEHS National Advisory

Environmental Health Sciences Council. Questions and discussions at the meeting explored options for analysis and decision-making in key areas.

- To continue the strategic dialogue, a "Strategic Planning Forum" was hosted by NIEHS on October 17 and 18, 2005, in Chapel Hill, North Carolina. The Forum was co-chaired by Dr. Frederica Perera, Professor of Environmental Health Sciences and Director of the Columbia Center for Children's Environmental Health at Columbia University's Mailman School of Public Health; and Dr. Gerald Wogan, Underwood-Prescott Professor of Toxicology Emeritus and Professor of Chemistry Emeritus at the Massachusetts Institute of Technology. Over 90 invited scientists, clinicians, and persons representing support and advocacy organizations participated in a highly interactive program involving intense, small-group discussion on six core topics related to future NIEHS priorities. Each discussion group was given specific issues and questions to consider in their respective topic area; was asked to reach a general consensus on their conclusions; and reported their outcomes at a plenary session that followed. The procedure was followed through three successive cycles to cover all six topics. Additionally, all participants were asked to list the proposed priorities they felt were most important in each topic area, following the plenary presentations. Questions were also posed at the conclusion of the meeting for the attendees' consideration and response.

- The substantial input from the Strategic Planning Forum was gathered and analyzed by NIEHS staff and advisors. Recommendations and subject area priorities were weighed, as were the detailed transcripts from every discussion group. Summaries from the discussion sessions were combined into a formal "Proceedings" of the Forum for distribution to attendees.

- Additional discussions were held in November with members of the NIEHS Public Interest Liaison Group (PILG) representing non-governmental medical, environmental, and policy organizations with interests in the Institute and the future direction of environmental health research, research applications, and policy. Emerging NIEHS scientific priorities were the central topic of the discussions.

- The draft NIEHS Strategic Plan was posted on the NIEHS website for public comment in December, 2005. Feedback from the website was gathered for consideration as the document continued to be revised.

- Key components of the NIEHS Strategic Plan were shared with staff at an all-hands meeting in January, 2006 hosted by the Institute Director.

- Following advanced distribution, the final proposed NIEHS Strategic Plan was presented to the NIEHS National Advisory Environmental Health Sciences Council at its February, 2006 meeting.

A New Outlook for Environmental Science and Health

Understanding the complex relationship between endogenous and exogenous risks within populations and affected individuals, how environmental exposures affect human biology, and how this knowledge can be used to reduce morbidity and extend longevity, is precisely the opportunity and challenge that faces the NIEHS. **The Vision of NIEHS is to use environmental sciences to understand human disease and improve human health.** This will be accomplished by supporting research and professional development in the environmental sciences (toxicology, relevant basic science), environmental medicine, and environmental public health. In addition to understanding how environmental exposures affect human biology, the fundamental goal of the NIEHS is to learn how this knowledge can be used to reduce morbidity and extend longevity.

Environmental exposures may adversely affect those who are vulnerable temporally (age, developmental stage), spatially (geographic location), or by unique circumstance (comorbid disease, nutritional status, socioeconomic status, genetics). We have mounting evidence that environmental agents contribute substantially to many diseases of great public health significance. Cancer, chronic lung disease, metabolic disorders, and neurodegenerative conditions: these diseases are all chief causes of mortality in the U.S. that are known to have significant environmental etiologies. Environmental effects on chronic, non-fatal conditions are also well-documented: birth defects, asthma, neurodevelopmental dysfunctions are all known to be linked to environmental exposures. Results from studies of twins reveal that development of chronic human disease owes as much or more to non-genetic, presumably environmental, components as it does to genes. Consider the following findings:

- In one study evaluating risk for developing several types of cancer, genes accounted for less than 50% of disease risk; environmental factors presumably played a role in the remainder cancer cases (Lichtenstein, et al., NEJM 2000; 343:78-85).
- In a review of several studies of autoimmune diseases, genetics appeared to account for 25% - 40% of disease risk, with environment accounting for the remaining 60% - 75% or risk (Powell, et al., EHP 1999; 107(S5):667-672).
- In a study of Parkinson's Disease, early onset (before age 50) appeared to be controlled predominantly by genetic factors. In the more common late onset cases, however, an environmental trigger was suspected of accounting for roughly 85% of the cases (Tanner, et al., JAMA 1999; 281:341-346).

Because environmental exposures contribute substantially to the etiology of many common and complex human diseases, the NIEHS is in a unique position to focus on the interface between environmental exposures, vulnerable populations, human biology and genetics, and the common diseases that limit our longevity. In the postgenomic era of biomedical research, the NIEHS can take a leadership role in improving human health by using environmental exposures to understand human biology and human disease: how genes work in biological systems, how genetic

variants contribute to the development of disease, and why individuals with the same disease have very different clinical outcomes.

Environmental exposures are often highly associated with diseases that contribute to the excess burden of poor health in disadvantaged communities. For this reason, research in environmental health sciences can offer important insights into how to reduce disparities in health between U.S. populations. The NIEHS has traditionally supported research relevant to understanding health disparities, and this focus will continue as the Institute moves forward.

To enable the field of environmental health sciences to have the greatest impact on preventing disease and improving human health, the NIEHS will be enhancing its efforts in four major areas. These are basic science, disease-oriented research, global environmental health, and training tomorrow's scientists. This Strategic Plan outlines the future shape of the NIEHS portfolio that will develop these four areas in order to maximize the benefits of our research investments for the nation's health.

Goal A: Foster environmental research in human health and disease. NIEHS is aiming to balance and integrate its investments in exposure-oriented research and disease-oriented research. Toward that end, NIEHS will encourage research that emphasizes the use of environmental exposures to inform pathophysiologic endpoints, thus optimizing the ability of its research to culminate in improved human health. Diseases for which environmental health sciences can provide important insight include (but are not limited to) such common disorders as: immune mediated diseases; neurodevelopmental disorders; neurodegenerative diseases such as late-onset Parkinson's Disease; cardiovascular diseases; and lung diseases, especially asthma.

- **Objective 1: Encourage research that emphasizes the use of environmental exposures to understand pathophysiologic endpoints that are relevant to common, complex diseases.** This approach offers one of the major benefits of environmental health science because different agents can evoke different pathophysiologic phenotypes having the same overt, clinical symptoms. Thus, in complex diseases such as asthma, individual responses to different environmental agents can help aggregate patients into discrete subtypes that can more effectively be evaluated for the specific pathogenic mechanisms that are causing symptoms. In this way, environmental agents can provide a tool to differentiate meaningfully among the numerous phenotypes, enabling researchers to distinguish the different underlying mechanisms of disease which can then lead to improved therapeutic interventions.

- **Objective 2: Develop improved *in vivo* models for human disease.** Comparative biology now offers new opportunities for *in vivo* models of human disease that enhance understanding of exposures and disease. Similarly,

genetic diversity among murine models provides opportunities to enhance our understanding of genetic susceptibility to environmental exposures, helping to identify key "master control systems," and improve our ability to extrapolate and translate findings to humans. Improved *in vivo* models could also be used to study the role of epigenetics in disease etiology, an area for which environmental influences might have a particularly strong impact. Finally, transgenic animals could help researchers conduct experiments in comparative biology, to identify conserved biological responses, to uncover new biological mechanisms, and to test the importance of genes in exposure response relationships.

- **Objective 3: Enhance the role of the physician scientist in environmental health sciences.** NIEHS has a lower percentage of physicians as principal investigators than most of the other NIH institutes. However, as we shift the focus of research supported by the NIEHS to emphasize human disease, the need for physician-scientists becomes compelling. While there are numerous examples of PhD-trained scientists who have had major effects on human health, MD-trained scientists are simply more familiar with the varied manifestations of human disease. In this context, physicians have the unique ability to focus their research on scientific questions that are clinically relevant. While physician-scientists may lead scientific projects or teams studying a particular disease, it is just as likely that they will serve as the "glue," helping a group of basic or public health investigators to focus their interests on clinically relevant areas of human pathophysiology.

Goal B: Use environmental toxicants to understand basic mechanisms in human biology. Environmental exposures provide a controlled method for targeting and manipulating cellular machinery in ways that provide insight into both basic biology and the mechanistic events leading to clinical disease. Because environmental agents often operate early in the disease process, they also provide a useful technique for identifying very early events in disease pathogenesis that can potentially be used both to identify methods to diagnose diseases before they are clinically evident and to develop early interventions that prevent progression to end-stage disease. In this way, environmental agents have tremendous potential for use as probes in understanding the processes of common chronic diseases, as well as suggesting possible routes for therapeutic intervention. There are a number of fundamental biological processes that have important implications in human health and for which environmental health research can generate insight.

- **Objective 1: Increase our understanding of epigenetic influences on health.** These are mechanisms outside of normal inheritable mechanisms that are particularly relevant to environmental health sciences and which may prove crucial in the interface between genes, environment, and disease. A number of environmental factors can substantially alter gene expression and generate developmental abnormalities or functional changes via alterations in genetic

programming or epigenetic control of gene expression. These changes in gene expression can cause or affect the risk of developing cancer, immunologic diseases, and other complex diseases. Epigenetic mechanisms are also important for understanding the developmental/fetal basis of adult disease. This is a temporal issue involving transgenerational inheritance, and is particularly important for cancer, diabetes/obesity, and infection/immune processes.

- **Objective 2: Expand our understanding of environmental influences on genome maintenance/stability and its impact on human health.** The study of DNA damage, repair, and maintenance is an important area of investigation, particularly with regard to aging, cancer, and cell death.

- **Objective 3: Improve our understanding of how signal transduction pathways work and how they influence disease.** Cellular communication pathways such as signal transduction are critical to understanding how the environment has effects on biological systems.

- **Objective 4: Increase our knowledge of the pathways involved in oxidative stress and inflammation, as well as the impact of these processes on common diseases.** These processes are increasingly being recognized as an important pathway by which gene-environment interaction modulates disease onset.

Goal C: Enhance integration of basic environmental sciences and more applied scientific approaches to understand disease pathogenesis and the distribution of disease. Such an approach will be needed to optimize our ability to integrate research from all levels of investigation and to promote a comprehensive understanding of the relationship between environmental agents and the biology underlying their contribution to health and disease. Thus, study of how an environmental agent affects a target at the molecular, cellular, or tissue level, could be related up and down a continuum of biological complexity that ultimately informs us about the etiology, pathogenesis, and distribution of disease.

- **Objective 1: Promote an interdisciplinary, integrative research approach**. The NIEHS should design and implement models for research that integrate patient-oriented or public health research with basic mechanistic studies to address disease etiology, pathogenesis, susceptibility and progression. By fostering such collaborative research, the NIEHS will (1) increase the relevance of basic scientific discoveries in environmental health sciences to human disease; and (2) move this knowledge into clinical and public health application to ultimately improve human health.

- **Objective 2: Encourage innovative, high-risk research by identifying and removing barriers to integrative research.** Integrative research requires

teams of investigators who are willing to cross the boundaries of their own discipline to develop research that they simply can't do on their own. The NIEHS will examine how the current structure of rewards and grants (training and funding mechanisms, peer review, and reward systems) can be changed to encourage creation of the non-traditional teams that will be needed to perform future environmental health research.

- **Objective 3: Foster collaborations that will improve and expand access of researchers to advanced technology.** There is a need for investment in resource-intensive technology, such as mass spectrometry and NMR for use in metabonomics and proteomics research. There are currently financial barriers to purchasing the necessary high-end instrumentation needed to support this objective. For this reason, NIEHS will foster efforts to coordinate and collaborate in the use of such expensive instruments, such as consortia among researchers and universities to improve and expand access to equipment.

Goal D: Develop a program in global environmental health. As the nation's premier environmental health research institute, the NIEHS has an opportunity and an obligation to address environmental health issues globally. NIEHS is investigating a number of mechanisms to provide greater focus and emphasis to this important area of research and is in the process of developing partnerships to better leverage resources in pursuit of new and emerging opportunities in global environmental research.

- **Objective 1: Focus on populations that are exposed to high levels of environmental agents.** NIEHS-supported scientists have long recognized the fact that exposures to environmental pollutants vary around the world and can offer fruitful avenues for defining the impact of the environment on human health. Studies on the higher levels of environmental exposure in other nations can lead to insight into potential health effects and can also offer unique opportunities for teasing apart different cellular pathways to the development of complex diseases. Use of newly developed technologies in exposure assessment and exposure biology will also facilitate this research, leading to greater understanding of disease risk, pathogenesis, and prevention.

- **Objective 2: Focus on diseases that are unevenly distributed and have a high impact on morbidity and mortality.** Variations in incidence of diseases offer clues that may suggest where environmental agents are contributing to disease pathogenesis. Research that follows up on these clues should target the most prevalent and severe diseases in order to have the greatest impact on improving public health.

- **Objective 3: Develop partnerships to conduct global environmental health research.** These partnerships can be with current national and international agencies, cohorts, and networks. NIEHS will also pursue the possibility of

forming a consortium of groups to focus on global issues in environmental health. Supported research efforts must contribute to the concept that successful global health research can only be done when both parties respect the other's needs, and when the partnerships are equal and benefits of the research accrue both to the researchers and the study population. For this reason cultural sensitivity will be a necessary component of study design. Cultural facets such as payment mechanisms, linguistics, religious traditions, health and disease beliefs, and gender roles should be taken into account when entering into partnerships and designing studies and intervention strategies, and should be communicated to the researchers involved.

- **Objective 4: Build capacity to pursue research in global environmental health.** NIEHS will pursue four avenues for increasing the current capacity of trained personnel and research infrastructure: (1) develop training opportunities for young investigators from other countries; (2) work with universities to develop regional environmental health centers designed to work in collaboration with NGOs and governments; (3) encourage NIEHS centers and SBRP to have international partners, a la the "Sister Cities" program; and (4) support opportunities for peer networking globally.

Goal E: Develop sensitive markers of environmental exposure, early (pre-clinical) biological response, and genetic susceptibility. Exposure assessment is currently the Achilles' heel of environmental health science. The methodology can often be weak and imprecise. In order to advance the field of environmental health sciences, it is critical to advance the area of environmental exposure assessment.

- **Objective 1: Develop validated biomarkers of exposure, susceptibility, and effect.** Ideally, these biomarkers would be accurate for timeframes of interest (such as previous or historical exposures), mechanistically linked to diseases of interest, and serve to link environmental exposures with biological effects. Integration across biomarkers is also needed so that relationships among disparate biological responses to exposures can be studied would be the ultimate goal of biomarker development. It would be particularly valuable to focus on a specific exposure-disease relationship and address it using multiple exposure assessment tools. There are several research areas with a critical need for specific biomarkers. These include gene expression markers, single-cell sequencing of acquired mutations, methylation status of DNA, and the ability to link gene expression data with biomonitoring data.

- **Objective 2: Develop new exposure technologies.** These technologies need to be cheaper, faster, and better than those currently available. Real time measurement of exposures, as well as quick turnaround and high throughput analysis of samples should be a hallmark of this goal. The NIEHS will capitalize on continued improvements in portability and sophistication of personal monitoring devices, field monitoring, and surveillance kits**.** Of

particular interest is the use of nanotechnology for low-cost, micro-scale characterization of environmental and potentially biological samples. NIEHS is also interested in developing the tools needed to better understand the bioavailability of toxicants during exposure.

- **Objective 3: Address institutional barriers to effective exposure assessment and toxicity assessment in humans.** Those areas for which NIEHS can play a role are:
    - Ethical issues surrounding exposure assessment studies in human populations, including confidentiality and IRB issues, study subject results reporting requirements (even in the absence of interventional or therapeutic strategies), identification of and access to appropriate exposed populations, particularly high-risk populations such as ethnic and minority populations, and access to sample materials, reliable medical data, and bio-repositories.
    - Standardization and validation in sampling methodologies, exposure assessment strategies and tools, and biomarkers and predictive models.
    - Improved bioinformatics to address the large datasets currently being generated and development of a methodology to relate among these datasets.
    - Current lack of clinical phenotypes, lack of suitably trained workforce, lack of availability of cost-effective and sensitive measurements of low-level exposures, difficulty linking existing exposure data with genetic susceptibility, and the need for microscale sample analyses

- **Objective 4: Apply imaging technologies to evaluate environmental exposures.** This is a potentially rich area for innovation in environmental health research since these technologies can be used to identify functional changes in exposure and effects (e.g., MRI to quantify manganese and iron in the brain). Accelerator mass spectrometry as an ultra-sensitive way to detect exposures is another promising technology, as is molecular imaging to investigate protein-protein interactions.

- **Objective 5: Develop better dose-response methodologies.** Dose-response methodology needs to be strengthened in (1) extrapolation of results from high-dose experiments to low-dose effects, (2) the ability to accurately measure and characterize low-dose responses, (3) cumulative exposures, chronic exposures, reduced exposures (through experimental trials and study of natural experiments), (4) amplified exposures (agents whose biological effects are amplified within the system), and (5) mixtures and complex exposures.

Goal F: Recruit and train the next generation of environmental health scientists. Environmental health scientists will need to be conversant in more than one discipline so that they're able to have the greatest impact on understanding human health and disease. In the future, the NIEHS will need to attract more physician-scientists into the field of environmental health so that the broad spectrum of environmentally associated

diseases can be more completely addressed. NIEHS must find a way to attract the best and brightest individuals into our field in order to ensure that the full promise of environmental health research is met.

- **Objective 1: Increase recruitment of talented students into environmental health sciences.** A variety of mechanisms will need to be pursued to increase the visibility of the field of environmental health sciences and to create incentives for recruitment, including: providing exciting field experiences for interested students; increasing the likelihood of funding for future researchers; better marketing of environmental health sciences at health fairs and scientific meetings; and creating customized approaches for attracting students at various points in the educational pipeline (high school, college, and graduate school).

- **Objective 2: Enhance opportunities for young students to actively participate in environmental health science research.** Motivated high-school and undergraduate students are at an important juncture in their life as they consider future career choices. NIEHS will provide innovative research opportunities for students in environmental health.

- **Objective 3: Engage the medical community in environmental health research.** This objective has two components. The first is to better incorporate environmental health science into medical school curricula and research so that future physicians are better equipped to appreciate the interaction of environment with human health. The second is to increase the cadre of physician-scientists within the field of environmental health research.

Goal G: Foster the development of partnerships between the NIEHS and other NIH institutes, national and international research agencies, academia, industry, and community organizations to improve human health. Environmental health science research, unlike most other fields, is not limited by an organ system, a methodological approach, a single disease, or a population. Its multidisciplinary nature offers great promise, but it also presents challenges since research activities are organized around disciplines and institutions that present barriers to collaborations across disciplines and missions. Public investments will be optimized by developing ways to integrate across these multiple disciplines and agencies.

- **Objective 1: NIEHS programs will be reoriented to foster collaborations across teams of scientists with complementary skills and areas of expertise.** This will enable the NIEHS to better address important research needs, as well as enabling the Institute to better align with cross-NIH efforts such as the NIH Roadmap (http://nihroadmap.nih.gov).

- **Objective 2: Provide leadership in developing access to important subject populations.** This leadership will include enhancing the stability/accessibility

of databases, repositories, and registries through partnerships with other organizations. These types of partnerships will also be brokered to provide more and better access to study populations through twin registries, occupational cohorts, and large cohorts that can not be assembled by a single agency. Through these partnerships, NIEHS will also investigate identification of high- and low-exposure populations that could be used in comparative studies. Partnerships could also be used to help develop tools to better assess social and economic inequities that are becoming increasingly important in understanding relative disease risks within a population.